CLINICAL CONFERENCE

FROM THE MEDICAL STAFF CONFERENCES OF THE UNIVERSITY OF CALIFORNIA HOSPITAL, SAN FRANCISCO, CALIFORNIA, MARCH 19, 1947

CASE PRESENTATION BY DOCTOR N. FOREMAN*: A white female, aged 42, was admitted to the hospital March 6. Her complaints were progressive weakness, fatigability and dyspnea for the preceding year and a half. In June of 1945 she noted the insidious onset of easy fatigue and a dull ache in the anterior portion of the neck, similar to that she had experienced following her first pregnancy 11 years before, and for which she had been given thyroid over a period of four years. In the fall of 1945 the BMR was normal, the hemoglobin was 50 per cent. She was given iron, liver extract, calcium and vitamins for the following year without much benefit. In November 1946 she was found to have protein in the urine and spent a month in bed, but had no remission of her symptoms. She was admitted to the East Oakland Hospital in January 1947 for bone x-rays and sternal puncture. The diagnosis of multiple myeloma was made. Stilbamidine therapy and a diet low in animal protein were begun. After considerable difficulty in cross-matching she was given one transfusion. She received ten injections of Stilbamidine of 150 mg. each. Additional symptoms were a 15 pound weight loss, continuous roaring in the left ear for a year, progressive impairment of vision, several bouts of spontaneous epistaxis and an increased tendency to show ecchymoses. In December of 1946 she began to have menorrhagia and metrorrhagia which has continued unabated. She also had noted sternal tenderness for three or four months.

On physical examination, temperature was 36.5° C., respirations 24, pulse 90, and blood pressure 120/70. In general she appeared to be a tanned but very pale woman somewhat younger than the stated age of 42. Skin and mucous membranes were pallid. Examination of the eyes revealed some impairment of vision. Prominent veins, scattered punctate hemorrhages and a few flame-shaped hemorrhages were found in the fundi. There were several discrete small lymph nodes in the post-cervical and supra-clavicular regions. The heart was enlarged one centimeter to the left of the midclavicular line. The spleen was palpable two finger-breadths below the left costal margin. The right kidney was easily palpable. Pelvic examination was negative. The skeletal system showed only sternal tenderness. Percussion of the extremities, ribs, skull, and pelvis did not elicit pain.

The red blood count was 1.41 million, hemoglobin 20 per cent (3 gm.), white blood count 5,300 with a normal differential. The smear showed marked hypochromia, a tendency toward anisocytosis, and occasional erythroblasts and normoblasts. The platelet count was 200,000. The bleeding time was 17 minutes, coagulation time 4 minutes. The urine contained Bence Jones protein. PSP excretion was less than 20 per cent in two hours. NPN was 70 mg. per 100 cc. blood. The serology was negative. The stool contained occult blood. The prothrombin time on entry was 29 per cent. The serum proteins were 9.48 gm. per 100 cc. of blood with albumin 2.25 gm. and globulin 7.23 gm. The only significant finding in the x-ray films was a rarefaction in the upper end of the right femur. Chest and skull films were normal except for slight cardiac enlargement.

The patient was given a diet low in animal protein, daily injections (150 mgm.) of Stilbamidine, Vitamin K, iron and blood transfusions. After a week of Vitamin K therapy, the prothrombin was only 31 per cent as compared with the preceding 29 per cent. The hemoglobin rose to 70 per cent; the NPN dropped to 60 mg. per 100 cc. A bromsulphalein test was within normal limits.

DR. STACEY METTIER†: One may question the diagnosis on history in this patient because it is not that which we usually see in patients with a characteristic multiple myeloma. The onset of illness has been rather insidious, finally leading up to a point where the patient goes to a physician because of symptoms referable to the anemia. In most cases of multiple myeloma the patient comes to the physician because of excruciating pain. The pain in multiple myeloma may be experienced by the patient in different parts of the body. On occasions, the diagnosis of rheumatic fever may be made because the pain migrates from one part of the body to another, and in these locations is associated with bone tenderness. Pain has not been an outstanding factor in this patient's illness. Another mode of onset is characterized by fracture of a bone. We have seen that happen to an individual who prior to the accident had been apparently well, when, suddenly, a slight injury, a misstep, or a fall has led to the fracture of an arm or leg, or the ribs.

The third type of onset is characterized by a hemorrhagic tendency. This patient has exhibited some tendency to bleed. I can't explain that clearly because we do not have the decrease in the platelets that one usually gets in association with the bleeding of multiple myeloma. She has a prothrombin deficiency, which offers opportunity for considerable speculation because we don't know how to account for it. Apparently her liver function is within normal limits. It may be that she is not absorbing Vitamin K from the intestinal tract. However, that is a side point and could be discussed at further length. So, there are certain things here against the diagnosis of multiple myeloma on the history alone.

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On physical examination, one would expect again to see a patient who exhibits suffering. I don't think there is any pain worse than bone pain, and especially that seen in multiple myeloma. At times it is difficult to control with large doses of narcotics. Bone tenderness is absent here except over the sternum, which is slightly in favor of multiple myeloma. Lymphadenopathy is found only in a very small percentage of patients in whom the spleen is palpable. Dr. Lowenhaupt recently published a paper showing the presence of the myeloma cells in the spleen. Occasionally they are found in the liver. On roentgen examination, we should expect to find multiple areas of decreased density in the bones if the illness has been present for a prolonged period of time as it has been here. We find one questionable area in the femur.

As far as laboratory diagnosis is concerned, one would say, "Well, we will establish the diagnosis on finding Bence-Jones protein in the urine." But I may assure you that Bence-Jones proteinuria may be found in other conditions, especially those where there is a space-consuming lesion in the bone marrow, and therefore that is not absolutely positive in establishing the diagnosis. The second most important laboratory procedure would be that of the hyperproteinemia, especially the globulinemia which is tremendously increased in most patients with multiple myeloma. There is no relationship between Bence-Jones proteinuria and the increased globulin content in the blood. There may be a high globulin content in blood plasma and not Bence-Jones protein in the urine. However, the combination of the increased globulin and Bence-Jones proteinuria again points toward a probable diagnosis of myeloma.

We may establish the diagnosis if we are lucky enough to procure myeloma cells in the sternal puncture. Preferably, we should do a sternal biopsy. In carrying out either one of these procedures, I wish to warn enthusiasts that this may be a very serious diagnostic procedure in a patient who has involvement of the outer plate of the sternum. In the presence of decalcification, the sternal plate may be very brittle and one may go through very readily either with the needle or with the scalpel.

This patient shows the presence of some abnormal cells in the bone marrow. I don't think they have been found in the peripheral blood. What are we going to call these cells? I would like to make a few more comments at this point concerning the type of cell that one finds in this peculiar disease. There are many who choose to call it a plasma cell because it does resemble the plasma cell that one finds normally in the tissue. If one does enough sternal punctures and examines the tissue, he may find a cell 10 to 12 micra in diameter. It is slightly oval in outline with a small eccentric nucleus. It has a so-called radiation of chromatic material, which is rather densely stained, and a clear greenish-blue cytoplasm. It is called a plasma cell. When one finds 5, 6, or 7 per cent of these cells in a specimen, does that constitute a diagnosis of multiple myeloma? I should say not necessarily, because at times we can see them increased under the strain of infection. However, there is a type of cell that is considerably larger than this one and may attain a size of 18 to 20 microns. The nucleus, again, is eccentric, but is larger in proportion to the amount of cytoplasm that is present. The nucleus takes a very deep, purplish stain that is almost pyknotic in character. It does not have the radiations one sees in the plasma cell. The cytoplasm is quite similar, but if you focus up and down on the cytoplasm very carefully, you may see that it appears almost vaculated with very tiny areas in which there is an absence of the stain.

Now, let's call this cell a myeloma cell in contrast to the plasma cell which is normal. Since we are speaking about this cell, the question arises as to its origin. If it is related to the plasma cell, one would expect to find a frequent occurrence of this tumor in lymphoid tissue. There are very few cases on record where myeloma cells have been reported in lymphoid tissue. Jackson and Parker reported a case in which there was involvement of lymphoid tissue in the tonsils. They felt they had a case of myeloma that was limited entirely to lymphoid tissue. I am reminded of one patient we had here a few years ago where we had involvement of the lymph nodes in the groin. But lymph node involvement is a very rare occurrence primarily in multiple myeloma. So it brings us back to the blood-forming tissue in the bone marrow.

Should we have suspected the presence of myeloma in this patient prior to the time that she came for her first examination by a physician? If a blood count is taken and the physician should go to the laboratory himself and examine the blood films, he might be struck by the type of anemia. It is usually normocytic and normochromic. There may be a depression of the platelets.

There is no specific therapy for multiple myeloma. We are disappointed in the use of roentgen irradiation, in irradiated phosphorous, and other forms of irradiation. Recently, we heard of Stilbamidine. I refer you to the article by I. Snapper, which appears in the Journal of the Mt. Sinai Hospital for September, 1946. It was learned that in kala azar, a disease in which the plasma globulin is high, administration of the material to the patient has a beneficial effect. Snapper reasoned that if it is effective in conditions with high blood protein it might have some effect on patients with increased globulinemia such as in multiple myeloma. In 1945, Dr. Snapper started treatment on a group of patients. He found favorable results in nine out of fourteen and no effect in five. The effect demonstrated was a relief of pain and a disappearance of the myeloma lesions in the bones which subsequently became calcified over a period of six months to one year. There was no effect on the Bence-Jones proteinuria; there was no reduction of the plasma globulin, but he felt justified in making his report simply on the basis of the relief of pain in the patient.